Polytronics for Biotronics: Unique Possibilities of Polymers in Biosensors and BioMEMS ?

Gábor Harsányi and Hunor Sántha

Department of Electronics Technology
Budapest University of Technology and Economics
Budapest, 1521, Hungary
Phone: +36-1-463-3634, Fax: +36-1-463-4118, e-mail: Harsanyi@eet.bme.hu

Abstract

In recent years, sensing polymeric materials have gained a wide theoretical interest and practical application in biomedicine both in sensors and in bio-MEMS. They can be used for very different purposes and may offer unique possibilities. The presentation and the paper give a broad summary about the polymer films used in these type applications. Polymers offer a lot of advantages for medical and biosensor technologies: they are relatively low cost materials, their fabrication techniques are quite simple, they can be deposited on various types of substrates using methods compatible with all microelectronic and micro fabrication technologies, as well as the wide choice of their molecular structure and the possibility to build in side chains, charged or neutral particles or even grains of specific behavior into the bulk material or on its surface region enables producing films with various physical and chemical properties including also sensing behavior.

1. Introduction

Although the practical application of biomedical sensors has been developing rapidly, the theoretical background of their operation is clarified only partly or not at all, in many cases. There are debates about the signal excitation mechanisms, signal conditioning methods, and the interpretation of practically measurable and theoretically expected results. Developing new sensors often means a considerable basic research in the same time. This is one of the main commercialization barriers of chemical and biosensors in the biomedical area.

A number of edited surveys and monographs have been published during recent years about bioinstrumentation, bioelectronics and biosensors. Some of them are listed in the references for giving for background reading.

2. Biosensors and Biomedical Sensors

Sensors are conventionally classified according to the quantity to be measured into the groups for the measurement of mechanical quantities, thermal quantities, electrostatic and magnetic fields and fluxes, radiation intensity, chemical quantities, biological quantities

Another *classification* is possible *according to the nature of interaction* giving the basis of operation in the groups of physical sensors, chemical sensors, and biosensors. Accordingly, a *biosensor* is such a sensor, which uses a living component or products of living things for measurement or indication. Thus, a blood-oxygen sensor is not a biosensor, although it measures a biologically important parameter; it simply is a chemical sensor in a special application. On the other hand, an enzyme reaction based alcohol sensor is a biosensor even when used for measuring concentration in solutions produced by the chemical industry. *Biomedical sensors* measure a parameter of a biological system and provide information in biomedicine. Thus, an implantable blood pressure sensor is a biomedical sensor, but not a biosensor.

3. Requirements for Commercial Use

Biomedical application fields mean special requirements and challenges for sensors, but they also give special possibilities that cannot be exploited in other application fields. The main areas may be distinguished as follows:

0-7803-7567-X/02/$17.00 ©2002 IEEE

- appliances for diagnosis: measuring or mapping a parameter at a given time
- monitoring devices for measuring parameters within a given period
- built-in controlling units containing not only sensors but actuators as well

Although present practical applications are almost entirely from the first two areas, one of the most important research tasks for biomedical sensor engineers is to develop controlling systems that can be implanted into human bodies and continuously operate for long periods of time to simulate the function of an internal organ or other controlling mechanism. Many chronic diseases of our age are resulted from the failed operation of one of the controlling systems of the human body (e.g., high blood pressure, diabetes, etc.). These diseases can be handled by medicines, but the real controlling function cannot be replaced in this way: the danger of overcompensation is always threatening, as for example, hypoglycemia with insulin ration in diabetes. The ideal treatment solution calls for a continuous blood glucose monitoring and a continuously controlled ration of insulin, always in the necessary amount.

When considering the requirements, it is very important whether the sensor element is applied inside the human body (invasively) for analyzing *in vivo* or outside for analyzing a sample *in vitro*. Different approaches should be applied for long-term operation of physical sensors and for relatively unstable chemical and biosensors.

Since the various possible application modes result in different requirements, these should be handled separately according to the following groups:

1. Appliances for medical imaging (CT, PET, ultrasound echo, etc.):

- They generally are computer/controlled, high-cost appliances.
- The cost of the sensing "head" (containing intelligent sensors, sensor arrays or multisensors) is relatively low.
- The cost of the sensor element is not a determining factor.
- High reliability, a long lifetime, and the interchangeability of the "head" is required.
- Integrated smart sensors and sensor arrays are needed.

2. Small appliances for clinical diagnosis and personal use, in measuring, or in continuous monitoring of physical parameters:

- These are low-cost, sometimes consumer-like appliances for a few years' use (e.g., digital thermometer, blood-pressure meter, pulse and breath monitoring devices).
- Low cost (in clinical invasive use disposable!) sensor elements are required.
- They should be interchangeable in many cases.
- Long-term operation is not needed: only for a period of continuous use (e. g. one day)
- A harsh chemical environment should be expected in blood and tissues.
- Multisensors for compensating interference effects are needed.
- Integrated sensors for long-distance signal transmission (sometimes telemetry) are desired.
- Miniaturization is essential for catheter-tip applications
- A number of biocompatibility problems have to be overcome.

3. Implanted chemical and biosensors for continuous monitoring and regulation:

- Low-cost, disposable, interchangeable sensors are needed.
- Integrated multisensors and actuators are desired.
- Stable long-term operation and reliability are severe requirements.
- Refreshment possibility should be available without re-calibration.

4. Applications of Polymers in Biomedical Sensors

In recent years, sensing polymeric materials have gained a wide theoretical interest and practical application in biomedicine both in sensors and in bio-MEMS. They can be used for very different purposes and may offer unique possibilities. Polymers offer a lot of advantages for medical and biosensor technologies: they are relatively low cost materials, their fabrication techniques are quite simple, they can be deposited on various types of substrates using methods compatible with all microelectronic and micro fabrication technologies, as well as the wide choice of their molecular structure and the possibility to build in side chains, charged or neutral particles or even grains of specific behavior into the bulk material or on its surface region enables producing films with various physical and chemical properties including also sensing behavior [1].

The various biomedical application fields and related detection techniques, sensing effects, sensor structures, and their present status are listed in the Table (without the demand of covering all available types) [2].

The most important application fields of sensing polymer films are following areas:

- Physical sensors with special polymer types and polymer composites for measuring mechanical

and thermal parameters (heart and breathing rate, ultrasound echo, thermal mapping).

- Chemical sensors for blood and tissue monitoring: ion-selective and gas sensors using ion-selective and/or perm selective polymeric membranes;
- Biosensors for blood analysis: bio-catalytic sensors and DNA chips using electroconducting polymers.

5. PRESENT STATUS AND DEVELOPMENT TRENDS

The wide variety of biomedical sensor applications is obvious from the table. Because of this wide variety, any statement about present status and potential development must be carefully adjusted according to the sensor type and its application technique. Although, therefore, it is rather difficult to draw general conclusions, some trends could be highlighted that are typical for particular sensor groups. From this aspect, physical sensors should be distinguished.

The rather well-described transduction effects of *physical sensors*, as well as the rapid and continuous development resulting in integrated smart sensors and sensor arrays with always better performances (such as signal-to-noise ratio, long term stability, reliability, etc.) and always lower cost, means that the potential application fields are gradually being invaded by them. Their application is concentrated mainly on the following areas:

Medical imaging appliances. The application of sensors enabled not only the practical realization and several generations of new types of appliances (such as ultrasound-echo, thermal mapping based on piezoelelectric and pyroelectric polymers like PVDF) but also the introduction of computer aided image processing into conventional imaging areas. Great progress can be predicted for the latter areas in the near future.

Small personal and portable electronic diagnostic devices (such as heart rate monitors, phonocardiograph, etc.). Their widespread, low-cost commercial availability is based mainly on the application of low cost PVDF, and PTFE electret based sensors. Electronic data storage and processing enabled the clinical or ambulatory monitoring of the measured parameters.

The situation is much more contradictory in connection with *chemical and biosensors*. Chemical and biosensor technologies can play an important role in the documentation and improvement of public health by finding application in areas where rapid detection, high sensitivity and specificity are important. Clinicians or patients also need a way to monitor the concentration of several key metabolites of the human body in many diseases. Great efforts have been made recently to extend the conventional clinical *in vitro* chemical analysis with the possibilities of chemical and biosensors. Although several hundreds of papers are published about research results, there are only a few well-defined areas where they have really found commercial applications:

Blood oxygen monitoring. Both intravascular and transcutaneous sensors have already been commercialized on the basis of semi permeable polymers, like PTFE, but their application is rather limited. The easy and reliable operation of noninvasive oxymeters, relying practically on physical sensors, retained physicians from using the former two techniques that are somewhat harmful and more risky.

Continuous in vivo monitoring of key metabolites. The sensors can operate inside the body for a given period and give information on an analyte concentration; this approach can be used to establish a real-time feedback control and treatment. The most important breakthrough has been made with glucose applying the sensors in microdialysis systems

Portable screening appliances for personal use or for fast screening tests performed by physicians. This area is also currently dominated by glucose testometers, however, the application of sensors has not replaced exclusively conventional photometry in such appliances. The main reason for this is that the possibilities of integrated multisensor based systems for multianalyte testing have not been exploited yet. Commercially available medical enzymatic biosensor production is fully (98%) dominated by glucose sensors [3, 4] The remaining portion is for lactate, urea, and creatinine. In these sensory systems the enzymes are immobilized in polymeric membranes or electroconducting polymers.

Affinity sensors. The greatest breakthrough of recent years is that two affinity sensor types have gained commercial success: SPR immunosensors for pharmaceutical research and DNA-chips for genetic diagnostics and research. Since they are applied for *in vitro* testing, the patient-contact problems do not limit their rapid adoption. For the electronically addressed immobilization and readout, the application of electroconducting polymers may offer special advantages.

REFERENCES

[1] Harsanyi, G., *Polymer Films in Sensor Applications*, Technomic, 1995.

[2] Harsanyi, G., *Sensors in Biomedical Applications*, Technomic, 2000.

[3] Turner, A. P. F., "Biosensors: past, present and future."(1996) http://www.cranfield.ac.uk/biotech/chinap.htm

[4] Wetall, H. H., "Chemical sensors and biosensors, update, what, where, when and how." *Biosensors & Bioelectronics*, Vol. 14, (1999) pp. 237-242.

Table 1. Detection techniques, sensing effects, sensor structures and their present status in various biomedical applications
[a] CA = Commercially Available, R&D = Research and Development

Blood, appl. field	Measurand	Sensor/measurement type	Basis of the sensing effect	Sensor structure	Present status
Body surface temperature image	temperature mapping	pyroelectric vidicon	pyroelectric	PVDF capacitor CCD with PVDF	CA CA, R&D[a]
Ultrasound imaging	ultrasound time of flight	Elcomers transmitter/receiver arrays	pyroelectric piezoelectric	PVDF capacitor array	CA
Blood vessel lesion	flow mapping	Doppler-sonography	piezoelectric	PVDF capacitor array PVDF capacitor	CA CA
Heart-rate, apnoe Breathing wave	pressure pulses	finger tip sensor, phonocardiograph	piezoelectric	PVDF capacitor	CA
Glucose in blood and tissues	glucose concentration	GOD based biosensors	catalytic reaction and transduction with products	electrochemical cells, GOD immobilized in polymers (PVA, PAA, PVA, PWMA, Nafion, PHEMA, PPy)	some types CA, others in R&D
Hearing aid	acoustic pressure	microphones	electret-based	PTFE capacitor	CA
Artificial limbs	tactile image	tactile sensor array	piezoresistive capacitive piezoelectric	resistor array with pyrex composites Mylar capacitor array PVDF capacitor array	R&D, some types CA CA
Joint angle	angular displacement	monitor gloves, etc.	piezoresistive	strain gage on PI electrode array on PI	CA CA, R&D
Bioelectric signals	electric impulses	pick-up electrodes	ion transduction effect	amperometric cells with	CA
Blood dissolved O_2	pO_2	Clark-amperometric cell transcutaneous Clark-cell optical-fiber	permeation through skin and membranes fluorescence	PTFE membranes electrode with dye entrapped in PS	CA
Blood dissolved CO_2	pCO_2	Stow-Severinghaus cell	permeation through skin and membranes	potentiometric cell, pH-ISFET with PHEMA	CA CA, R&D
Blood acidity	pH	electrochemical optical-fiber	H^+-ion-complexation in membranes colorimetric effect fluorescence	potentiometric cell with ionophores embedded in PVC membranes electrode with dye entrapped in PAA	CA CA R&D
Ionic compounds in blood	Na^+, K^+, Ca^{2+}, Mg^{2+}, CT, NH_4^+ concentrations	electrochemical	ion-complexation in membranes	potentiometric cells, ISFETs ionophores embedded in PVC	CA, R&D
Gastric acidity	pH	electrochemical optical-fiber	ion-complexation	potentiometric, ISFET ionophores embedded in PVC	CA, R&D

Sweat analysis	Na⁺/Cl⁻ concentration	electrochemical	ion-complexation	Na⁺/Cl⁻ ISFETs with PVC membranes	mainly R&D	R&D
Metabolites and other substrates in blood	urea, uric acid, lactate, cholesterol, ATP etc.	enzymatic biosensors	catalytic reactions and transduction with products	electrochemical cells, electrodes with enzymes immobilized in polymers	mainly R&D, some types CA	R&D
Immunoreaction reading	antigens/antibodies	immunosensors	chemical affinity + labelled or direct sensing	electrochemical, gravimetric, with antigens and antibodies immobilized in polymers	mainly R&D some types CA	R&D
Macromolecules in blood and tissues	DNA	DNA-chips	chemical affinity + labelled or direct sensing	fluorescent or enzymatic readout of hybridized DNA sequences immobilized in BCPs	CA R&D	R&D

Resolution of the acronyms used in the Table

ATP	Adenosine-5'-triphosphate
CCD	Charge Coupling Device
DNA	Desoxyribonucleinic Acid
ECP	Electroconducting Polymer
GOD	Glucose Oxidase
IR	Infrared
ISFET	Ion-Selective FET
pCO_2	Partial pressure of carbon dioxide
pO_2	Partial pressure of oxygen
PAA	Polyacrylamide
PHEMA	Poly(hydroxyethyl methacrylate)
PMePy	poly(N-methylpyrrol)
PMMA	Poly(methyl methacrylate)
PPy	Polypyrrole
PS	Polystyrene
PTFE	Polytetrafluoroethylene
PVA	Poly(vinyl alcohol)
PVC	Poly(vinyl chloride)
PVDF	Poly(vinylidene fluoride)